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Abstract

In this paper we study a model of HCV with mitotic proliferation, a saturation infection rate and a discrete intracellular delay: the delay corresponds to the time between infection of a infected target hepatocytes and production of new HCV particles. We establish the global stability of the infection-free equilibrium and existence, uniqueness, local and global stabilities of the infected equilibrium, also we establish the occurrence of a Hopf bifurcation. We will determine conditions for the permanence of model, and the length of delay to preserve stability. The unique infected equilibrium is globally-asymptotically stable for a special case, where the hepatotropic virus is non-cytopathic.

We present a sensitivity analysis for the basic reproductive number. Numerical simulations are carried out to illustrate the analytical results.

Keywords: Local Stability, Hopf Bifurcation, Global Stability, Permanence, Sensitivity Analysis

1 Introduction

The mathematical theory of viral infections has been around during the last decades. This theory has proven to be valuable on the understanding of the dynamics of viral infections and in the evaluation of effectiveness of antiviral therapy. The most studied viruses in the mathematical theory of viral infections are human immunodeficiency virus (HIV), hepatitis C virus (HCV), human T-lymphotropic virus type 1 (HTLV-1) and hepatitis B virus (HBV).

In the mathematical theory of viral infections the basic models are concentrated on two steps of the lytic cycle: viral entry and release. One of the most well-known models for viral dynamics includes only three state variables, one variable for uninfected target cells, a second variable for infected cells, and a third variable for virions or free virus particles [16, 17, 18]. The basic model of viral dynamics that has been formulated by Neumann and co-workers [16] for HCV dynamics and this has been applied to the analysis of response to antiviral therapy. The ordinary differential equations (ODE) model is as follows:

$$\begin{aligned}\dot{T}(t) &= s - dT(t) - (1 - \eta)bV(t)T(t), \\ \dot{I}(t) &= (1 - \eta)bV(t)T(t) - \mu I(t), \\ \dot{V}(t) &= (1 - \epsilon)pI(t) - cV(t),\end{aligned}$$

Here $x(t)$, $y(t)$ and $v(t)$ denote the concentration of uninfected hepatocytes (or target hepatocytes), infected hepatocytes and virions or free virus particles, respectively. All parameters are assumed to be positive constants. Here, target cells are generated at a constant rate s and die at rate d per uninfected cell. These

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cells are infected at rate b per target cell per virion. Infected cells die at rate μ per cell by cytopathic effects. Because of the viral burden on the virus-infected cells, we assume that $d \leq \mu$. Parameter p represents the average rate at which the hepatitis C virus are produced by infected cells and c is the clearance rate of virus particles. Parameter η is the efficiency of drug therapy in preventing new infections, and ϵ is the efficiency of drug therapy in inhibiting viral production.

The intracellular viral life-cycle is an important process to consider in mathematical models. In the mathematical theory of viral infections, the intracellular delays of viral life cycle are modelled by delay differential equations. This class of models are concentrated on two intracellular delays: The first delay represents the time between viral entry into a uninfected-target cell and the production of new virus (See, [2, 3, 8, 10, 13, 29]) and the second delay corresponds to the time necessary for a newly produced virus to become infectious virus particles (See, [10, 23, 26, 29]).

The first model that included a intracellular delay was developed by Herz and co-workers [8], this model incorporate the delay between the time a cell is infected and the time it starts producing virus. Subsequently, Li and Shu [14] studied the global stability of the associated equilibrium points for this delayed system. Tam [23] suggested an virus dynamics model with virus production delay. Zhu and Zuo [29] studied the basic model of viral infections with two intracellular delays: cell infection and virus production. Huang, Takeuchi and Ma [10] derived a class of within-host virus models with a nonlinear incidence rate and discrete intracellular delays, followed by its global analysis.

The basic model of viral infections [8, 14, 29] assumes a source of uninfected cells but ignores mitotic proliferation of uninfected cells or infected cells. Later on, Dahari and co-workers [4, 5] for hepatitis C viral, extending the basic model [16, 17, 18] include mitotic proliferation terms for both uninfected and infected hepatocytes. Here they assume that the proliferation of cells due to mitotic division obeys a logistic growth law. The mitotic proliferation of uninfected cells is described by $aT \left(1 - \frac{T(t)+I(t)}{T_{\max}}\right)$. New infectious transmission occurs at a rate $bT(t)V(t)$, while new mitotic transmission occurs at a rate $aI(t) \left(1 - \frac{T(t)+I(t)}{T_{\max}}\right)$. Both infected and uninfected cells can proliferate with maximum proliferation rate a , as long as the total number of cells, $T(t) + I(t)$, is less than T_{\max} . The ODE model is as follows:

$$\begin{aligned}\dot{T}(t) &= s + aT \left(1 - \frac{T(t) + I(t)}{T_{\max}}\right) - dT(t) - (1 - \eta)bT(t)V(t), \\ \dot{I}(t) &= (1 - \eta)bT(t)V(t) + aI(t) \left(1 - \frac{T(t) + I(t)}{T_{\max}}\right) - \mu I(t), \\ \dot{V}(t) &= (1 - \epsilon)pI(t) - cV(t).\end{aligned}$$

In other words, the hepatitis model includes mitotic proliferation of uninfected cells, and mitotic transmission of infection through infected cell division. Also, this model assumed that infection could occur instantaneously once a virus contacted a target cell to infect a uninfected target cell. Hu and co-workers [9] introduced a discrete time delay to the hepatitis model to describe the time between infection of a hepatocyte and the emission of viral particles. Subsequently, Vargas-De-León [25] studied the parameter conditions for global stability of hepatitis model with mitotic proliferation for both uninfected and infected hepatocytes. The hepatitis model given in [4, 5] without delay, coincides with the HIV model studied in [27] for which the global stability analysis was completed.

In several of models with or without delay described above, the process of cellular infection by free virus particles are typically modelled by mass action principle, that is to say, the infection rate is assumed to occur at a rate proportional to the product of the abundance of free-virus particles and uninfected target cells. This principle is insufficient to describe the cellular infection process in detail, and some nonlinear infection rates were proposed. Li and Ma [13] and Song and Neumann [22] considered a virus dynamics model with monod functional response, $bT(t)V(t)/(1 + \alpha V(t))$. Regoes, Ebert, and Bonhoeffer [19] and Song and Neumann [22] considered a virus dynamics model with the nonlinear infection rates $bT(t)((V(t)/\kappa)^p)/(1 + (V(t)/\kappa)^p)$

and $bT(t)(V(t))^q/(1 + \alpha(V(t))^p)$ where $p, q, \kappa > 0$ are constants, respectively. Recently Huang, Takeuchi and Ma [10] considered a class of models of viral infections with an nonlinear infection rate and two discrete intracellular delays, and assumed that the infection rate is given by a general nonlinear function of the abundance of free-virus particles and uninfected target cells, $F(T(t), V(t))$, where the function $F(T(t), V(t))$ satisfies the concavity with respect to the abundance of free-virus particles. Such condition is satisfied by several well known infection rates. The DDE model given in [10] without delay is studied by Korobeinikov in [11].

Motivated by the above comments, in the present paper, we proposed a model more realistic by using an infection rate that saturates and a discrete intracellular delay. We consider the following delay differential equation (DDE) model

$$\begin{aligned}\dot{T}(t) &= s - dT(t) + aT(t) \left(1 - \frac{T(t) + I(t)}{T_{\max}}\right) - \frac{bT(t)V(t)}{1 + \alpha V(t)}, \\ \dot{I}(t) &= \frac{bT(t-\tau)V(t-\tau)}{1 + \alpha V(t-\tau)} + aI(t) \left(1 - \frac{T(t) + I(t)}{T_{\max}}\right) - \mu I(t), \\ \dot{V}(t) &= pI(t) - cV(t).\end{aligned}\tag{1}$$

The assumptions are the following. We assume that the contacts between viruses and uninfected target cells are given by an infection rate $bT(t)V(t)/(1 + \alpha V(t))$, it is reasonable for us to assume that the infection has a maximal rate of b/α . On the other hand, to account for the time between viral entry into an uninfected target cell and the production of an actively infected target cell, we introduce a time delay τ that represents the time from entry to production of new virus.

From the point of view of applications, the study of the asymptotic stability of equilibria, the permanence and the existence of orbit periodic are interesting topics in biological models. Particularly, the qualitative analysis of the models reveals the existence of scenarios possible of a viral infection. A first scenario is that the viral population is eventually totally cleared. Mathematically, this means that the infection-free equilibrium state is asymptotically stable. Biologically, the permanence characterizes that the virus is not cleared. The permanence take care of the second and third scenarios, which will be described below. A second scenario is that the infection becomes established, and that the virus population grows with damped oscillations, or unimodal growth, that is the infected equilibrium state (interior equilibrium with all components positive) is asymptotically stable. A third scenario is that the virus population grows with self-sustained oscillations, is that the interior equilibrium state is unstable.

In this paper, we shall study the possible scenarios of virus dynamic model (1). The paper is organized as follows. In section 2, we establish the positivity of solutions. In the section 3 we prove the existence of the equilibria, we perform the local stability analysis and the global analysis. The Hopf bifurcation analysis is presented in section 4. Conditions for the permanence are establish in section 5. In section 6, we perform an estimation of the length of delay to preserve stability. The numerical validation is found in section 7, a sensitivity analysis is presented in section 8 and finally we draw a conclusion in section 9.

2 Positivity of solutions

We denote the Banach space of continuous functions $\phi : [-\tau, 0] \rightarrow \mathbb{R}$ with norm

$$\|\phi\| = \sup_{-\tau \leq \theta \leq 0} \{|\phi_1|, |\phi_2|, |\phi_3|\},$$

by \mathcal{C} , where $\phi = (\phi_1, \phi_2, \phi_3)$. Further, let

$$\mathcal{C}_+ = \{(\phi_1, \phi_2, \phi_3) \in \mathcal{C} : \phi_i \geq 0 \text{ for all } \theta \in [-\tau, 0], i = 1, 2, 3\}.$$

The initial conditions for system (1) are

$$T(\theta) = \phi_1(\theta) \geq 0, I(\theta) = \phi_2(\theta) \geq 0, V(\theta) = \phi_3(\theta) \geq 0, \theta \in [-\tau, 0], \quad (2)$$

where $\phi = (\phi_1, \phi_2, \phi_3)$.

Lemma 1. *All solutions of system (1) with initial conditions (2) are positive.*

Proof. We prove the positivity by contradiction. Suppose $T(t)$ is not always positive. Then, let $t_0 > 0$ be the first time such that $T(t_0) = 0$. From the first equation of (1) we have $\dot{T}(t_0) = s > 0$. By our assumption this means $T(t) < 0$, for $t \in (t_0 - \epsilon, t_0)$, where ϵ is an arbitrary small positive constant. Implying that exist $t'_0 < t_0$ such that $T(t'_0) = 0$ this is a contradiction because we take t_0 as the first value which $T(t_0) = 0$. It follows that $T(t)$ is always positive.

We now show that $I(t) > 0$ for all $t > 0$. Otherwise, if it is not valid, nothing that $I(0) > 0$ and $I(t) > 0$, $(-\tau \leq t \leq 0)$, then there exist a t_1 such that $I(t_1) = 0$. Assume that t_1 is the first time such that $I(t) = 0$, that is, $t_1 = \inf\{t > 0 : I(t) = 0\}$.

Then $t_1 > 0$, and from system (1) with (2), we get

$$\dot{I}(t_1) = \begin{cases} \varphi_1(t_1 - \tau)\varphi_3(t_1 - \tau) > 0, & \text{if } 0 \leq t_1 \leq \tau, \\ T(t_1 - \tau)V(t_1 - \tau) > 0, & \text{if } t_1 > \tau. \end{cases}$$

Thus, $\dot{I}(t_1) > 0$. Thus, for sufficiently small $\epsilon > 0$, $\dot{I}(t_1 - \epsilon) > 0$. But by the definition of t_1 , $\dot{I}(t_1 - \epsilon) \leq 0$. Again this is a contradiction. Therefore, $I(t) > 0$ for all t .

In the same way, we see that $V(t)$ is always positive. Thus, we can conclude that all solutions of system (1) and (2) remain positive for all $t > 0$. \square

3 Stability Analysis

3.1 Equilibrium

To obtain the equilibrium points we look for constant solutions for system (1), and we obtain $E_1(T_0, 0, 0)$ and $E_2(T_2, I_2, V_2)$, where

$$T_0 = \frac{T_{\max}}{2a} \left(a - d + \sqrt{(a - d)^2 + \frac{4as}{T_{\max}}} \right), \quad (3)$$

The equilibrium point (T_2, I_2, V_2) satisfies

$$\begin{aligned} 0 &= s - dT_2 + aT_2 \left(1 - \frac{T_2 + I_2}{T_{\max}} \right) - \frac{bT_2I_2}{1 + \alpha V_2} \\ 0 &= \frac{bT_2V_2}{1 + \alpha V_2} - \mu I_2 + aI_2 \left(1 - \frac{T_2 + I_2}{T_{\max}} \right) \\ 0 &= pI_2 - cV_2. \end{aligned} \quad (4)$$

The third equation leads to $V_2 = \frac{pI_2}{c}$, which allows us to reduce system (4) to two equations, defining

$$\tilde{\alpha} = \frac{\alpha p}{c} \text{ and } \tilde{b} = \frac{bp}{c}.$$

We express the first equation of (4) as the following quadratic equation in T_2 :

$$\frac{a}{T_{\max}} T_2^2 + \left(d - a + \frac{aI_2}{T_{\max}} + \frac{bI_2}{1 + \tilde{\alpha}I_2} \right) T_2 - s = 0.$$

Note that this quadratic equation has two real roots of opposite sign that depend on I_2 . We are interested in the positive one, which is clearly a function of I_2 .

Defining $T_2 = f(I_2)$, we express the first two equations of system (4) as

$$\begin{aligned} 0 &= s - df(I_2) + af(I_2) \left(1 - \frac{f(I_2) + I_2}{T_{\max}}\right) - \frac{\tilde{b}f(I_2)I_2}{1 + \tilde{\alpha}I_2} \\ 0 &= \frac{\tilde{b}f(I_2)I_2}{\mu(1 + \tilde{\alpha}I_2)} - I_2 + \frac{a}{\mu}I_2 \left(1 - \frac{f(I_2) + I_2}{T_{\max}}\right). \end{aligned} \quad (5)$$

To compute the infection-free equilibrium we assume $I_2 = V_2 = 0$, and we obtain

$$T_0 = f(0) = \frac{T_{\max}}{2a} \left((a - d) + \sqrt{(a - d)^2 + \frac{4as}{T_{\max}}} \right).$$

Now if we consider the infected equilibrium, then $I_2 > 0$. From the second equation of (5) we can define

$$F(I_2) = \frac{\tilde{b}}{\mu} \frac{f(I_2)}{1 + \tilde{\alpha}I_2} + \frac{a}{\mu} \left(1 - \frac{f(I_2) + I_2}{T_{\max}}\right).$$

Considering that $f(0) = T_0$, then

$$F(0) = \frac{\tilde{b}}{\mu}T_0 + \frac{a}{\mu} \left(1 - \frac{T_0}{T_{\max}}\right) = R_0 = \frac{D}{\mu},$$

where $D = \tilde{b}T_0 + a \left(1 - \frac{T_0}{T_{\max}}\right)$.

We can rewrite the second equation of (5) as $F(I_2) = 1$.

Geometrically, we can interpret that equation as the intersections of the graph of the function $F(I_2)$ with the line $F = 1$ in the plane determined by F and I_2 . In order to have a biologically feasible infected equilibrium, the intersections to be considered are those in the first quadrant of that plane. Now, if the slope of the tangent line along the graph of the function $F(I_2)$ is negative and does not approach zero as I_2 increases beginning at $I_2 = 0$, as well as $F(0) > 1$, then there is only one of such intersections in the first quadrant, meaning a unique biologically feasible infected equilibrium. Now.

$$\begin{aligned} F'(I_2) &= \frac{\tilde{b}}{\mu} \frac{f'(I_2)}{1 + \tilde{\alpha}} - \frac{\tilde{b}\tilde{\alpha}f(I_2)}{\mu(1 + \tilde{\alpha}I_2)^2} - \frac{a}{\mu} \frac{f'(I_2)}{T_{\max}} - \frac{a}{\mu T_{\max}} \\ &= \frac{1}{\mu} \left(\frac{\tilde{b}}{1 + \tilde{\alpha}I_2} - \frac{a}{T_{\max}} \right) f'(I_2) - \frac{1}{\mu} \left(\frac{\tilde{b}\tilde{\alpha}f(I_2)}{(1 + \tilde{\alpha}I_2)^2} + \frac{a}{T_{\max}} \right) \end{aligned}$$

Note that $F'(I_2)$ depends on $f'(I_2)$. To calculate $f'(I_2)$ we first rewrite the first equation of (5) as

$$0 = \frac{s}{f(I_2)} - d + a \left(1 - \frac{f(I_2) + I_2}{T_{\max}}\right) - \frac{bI_2}{1 + \tilde{\alpha}I_2}.$$

Using implicit differentiation we get

$$f'(I_2) = - \left(\frac{a}{T_{\max}} + \frac{\tilde{b}}{(1 + \tilde{\alpha}I_2)^2} \right) \left(\frac{a}{T_{\max}} + \frac{s}{f^2(I_2)} \right)^{-1} < 0$$

then

$$\begin{aligned}
F'(I_2) &= \frac{1}{\mu} \left(\left(\frac{a}{T_{\max}} \right)^2 - \left(\frac{\tilde{b}}{1 + \tilde{\alpha}I_2} \right)^2 \right) \left(\frac{a}{T_{\max}} + \frac{s}{f^2(I_2)} \right)^{-1} - \frac{1}{\mu} \left(\frac{\tilde{b}\tilde{\alpha}f(I_2)}{(1 + \tilde{\alpha}I_2)^2} + \frac{a}{T_{\max}} \right) \\
&< \frac{1}{\mu} \left(\frac{a}{T_{\max}} \right)^2 \left(\frac{a}{T_{\max}} + \frac{s}{f^2(I_2)} \right)^{-1} - \frac{1}{\mu} \left(\frac{\tilde{b}\tilde{\alpha}f(I_2)}{(1 + \tilde{\alpha}I_2)^2} + \frac{a}{T_{\max}} \right) \\
&< \frac{1}{\mu} \left(\frac{a}{T_{\max}} \right)^2 \left(\frac{a}{T_{\max}} \right)^{-1} - \frac{1}{\mu} \left(\frac{\tilde{b}\tilde{\alpha}f(I_2)}{(1 + \tilde{\alpha}I_2)^2} + \frac{a}{T_{\max}} \right) \\
&= -\frac{1}{\mu} \frac{\tilde{b}\tilde{\alpha}f(I_2)}{(1 + \tilde{\alpha}I_2)^2} < 0.
\end{aligned}$$

Note that the minimum value that the denominator $\left(\frac{a}{T_{\max}} + \frac{s}{f^2(I_2)} \right)$ can take is

$$\left(\frac{a}{T_{\max}} + \frac{s}{f^2(0)} \right) = \left(\frac{a}{T_{\max}} + \frac{s}{T_0^2} \right) > \frac{a}{T_{\max}}.$$

Hence $F'(I_2)$ is negative and does not approach zero as I_2 increases. If, in addition $R_0 > 1$, then $F(0) > 1$ and the slope of the tangent line along the graph of the function $F(I_2)$ is negative and does not approach zero as I_2 increases beginning at $I_2 = 0$. It follows that the infected equilibrium exists and it is unique if $R_0 > 1$. Where

$$R_0 = \frac{1}{\mu} \left[\frac{bpT_0}{c} + a \left(1 - \frac{T_0}{T_{\max}} \right) \right] \quad (6)$$

as in [6]

3.2 Local Analysis

In this section we study the local stability of the infection-free equilibrium E_1 and the infected equilibrium E_2 .

The characteristic equation of system (1) at the infection-free equilibrium is of the form

$$\left(\lambda + d - a + \frac{2aT_0}{T_{\max}} \right) \left(\lambda^2 + \left(c + \mu - a + \frac{aT_0}{T_{\max}} \right) \lambda + c(\mu - a) + \frac{acT_0}{T_{\max}} - bpT_0e^{-\lambda\tau} \right) \quad (7)$$

we also consider that E_1 satisfies system (1), so $a \left(1 - \frac{T_0}{T_{\max}} \right) = d - \frac{s}{T_0}$. And using the previous fact we can rewrite the factors of the characteristic equation (7) as

$$\lambda = a - d - \frac{2aT_0}{T_{\max}} = - \left(\frac{s}{T_0} + \frac{aT_0}{T_{\max}} \right)$$

which have a negative eigenvalue, and the others eigenvalues are given by

$$\lambda^2 + a_1\lambda + a_0 + b_0e^{-\lambda\tau} = 0 \quad (8)$$

where

$$\begin{aligned}
a_1 &= c + \mu - d + \frac{s}{T_0}, \\
a_0 &= c(\mu - d) + \frac{cs}{T_0}, \\
b_0 &= -bpT_0
\end{aligned}$$

Let

$$f(\lambda) = \lambda^2 + a_1\lambda + a_0 + b_0e^{-\lambda\tau}$$

note that

$$\begin{aligned} a_0 + b_0 &= -\frac{1}{c} \left[\frac{bpT_0}{c} + d - \frac{s}{T_0} - \mu \right] = -\frac{1}{c} \left[\frac{bpT_0}{c} + a \left(1 - \frac{T_0}{T_{\max}} \right) - \mu \right] \\ &= -\frac{\mu}{c} (R_0 - 1) \end{aligned}$$

if $R_0 > 1$, and we consider λ real we have that

$$f(0) = a_0 + b_0 < 0 \text{ and } \lim_{\lambda \rightarrow \infty} f(\lambda) = \infty.$$

Hence exist a positive root λ^* of $f(\lambda)$, therefore the characteristic equation (7) has a positive root and the infection-free equilibrium is unstable.

When $\tau = 0$ the equation (8) becomes

$$\lambda^2 + a_1\lambda + a_0 + b_0 = 0,$$

with $a_1 > 0$ and, if $R_0 < 1$, we have $a_0 + b_0 > 0$. Hence, the equilibrium E_1 is locally asymptotically stable when $\tau = 0$.

If $\lambda = i\omega$ ($\omega > 0$) is a solution of (8) then separating in real and imaginary parts we obtain the system

$$\begin{aligned} a_0 - \omega^2 &= -b_0 \cos(\omega\tau), \\ a_1\omega &= b_0 \sin(\omega\tau), \end{aligned}$$

squaring and adding the last two equations and after simplifications we get

$$\omega^4 + (a_1^2 - 2a_0)\omega^2 + a_0^2 - b_0^2 = 0, \quad (9)$$

if $R_0 < 1$ the equation (9) has no positive roots. Noting that the equilibrium E_1 is locally asymptotically stable when $\tau = 0$, by the theory on characteristic equations of delay differential equations from Kuang [12], we see that if $R_0 < 1$, E_1 is locally asymptotically stable.

The characteristic equation of system (1) on the infected equilibrium E_2 is given by the following determinant

$$\det \begin{pmatrix} a - d - \frac{a}{T_{\max}}[2T_2 + I_2] - \frac{bV_2}{1+\alpha V_2} - \lambda & -\frac{a}{T_{\max}}T_2 & -\frac{bT_2}{(1+\alpha V_2)^2} \\ \frac{bV_2}{1+\alpha V_2}e^{-\lambda\tau} - \frac{a}{T_{\max}}I_2 & a - \mu - \frac{a}{T_{\max}}[T_2 + 2I_2] - \lambda & \frac{bT_2}{(1+\alpha V_2)^2}e^{-\lambda\tau} \\ 0 & p & -c - \lambda \end{pmatrix}$$

that can be rewritten as

$$\det \begin{pmatrix} -\left(\rho + \frac{a}{T_{\max}}T_2 + \frac{bV_2}{1+\alpha V_2}\right) - \lambda & -\frac{a}{T_{\max}}T_2 & -\frac{bT_2}{(1+\alpha V_2)^2} \\ \frac{bV_2}{1+\alpha V_2}e^{-\lambda\tau} - \frac{a}{T_{\max}}I_2 & -\left(\frac{bT_2V_2}{(1+\alpha V_2)I_2} + \frac{a}{T_{\max}}I_2\right) - \lambda & \frac{bT_2}{(1+\alpha V_2)^2}e^{-\lambda\tau} \\ 0 & p & -\frac{pI_2}{V_2} - \lambda \end{pmatrix}$$

and the characteristic equations is of the form

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 + (b_1\lambda + b_0)e^{-\lambda\tau} = 0 \quad (10)$$

where

$$\begin{aligned}
a_2 &= \rho + \frac{aT_2}{T_{\max}} + \frac{bV_2}{1 + \alpha V_2} + \frac{bT_2V_2}{(1 + \alpha V_2)I_2} + \frac{aI_2}{T_{\max}} + \frac{pI_2}{V_2} > 0 \\
a_1 &= \left(\rho + \frac{aT_2}{T_{\max}} + \frac{bV_2}{1 + \alpha V_2} \right) \left(\frac{bT_2V_2}{(1 + \alpha V_2)} + \frac{aI_2}{T_{\max}} \right) + \frac{pI_2}{V_2} \left(\rho + \frac{aT_2}{T_{\max}} + \frac{bV_2}{1 + \alpha V_2} \right) \\
&\quad + \frac{pI_2}{V_2} \left(\frac{bT_2V_2}{(1 + \alpha V_2)I_2} + \frac{aI_2}{T_{\max}} \right) - \frac{aT_2}{T_{\max}} \frac{aI_2}{T_{\max}} > 0 \\
a_0 &= \left(\rho + \frac{aT_2}{T_{\max}} + \frac{bV_2}{1 + \alpha V_2} \right) \left(\frac{bT_2V_2}{(1 + \alpha V_2)I_2} \right) \frac{pI_2}{V_2} - \frac{pbT_2}{(1 + \alpha V_2)^2} \frac{aI_2}{T_{\max}} - \frac{aT_2}{T_{\max}} \frac{pI_2}{V_2} \frac{aI_2}{T_{\max}} \\
b_1 &= \frac{aT_2}{T_{\max}} \frac{bV_2}{1 + \alpha V_2} - \frac{pbT_2}{(1 + \alpha V_2)^2} \\
b_0 &= \frac{aT_2}{T_{\max}} \frac{pI_2}{V_2} \frac{bV_2}{1 + \alpha V_2} + \frac{pbT_2}{(1 + \alpha V_2)^2} \frac{bV_2}{1 + \alpha V_2} - \frac{pbT_2}{(1 + \alpha V_2)} \left(\rho + \frac{aT_2}{T_{\max}} + \frac{bV_2}{1 + \alpha V_2} \right)
\end{aligned}$$

with T_2, I_2, V_2 defined in (3).

When $\tau = 0$ equation (10) becomes

$$\lambda^3 + a_2\lambda^2 + (a_1 + b_1)\lambda + (a_0 + b_0) = 0$$

by the Routh–Hurwitz criterion the conditions for $\text{Re}\lambda < 0$ are $a_2 > 0$, $a_0 + b_0 > 0$, $a_2(a_1 + b_1) - (a_0 + b_0) > 0$, in our case $a_2 > 0$ and

$$\begin{aligned}
a_0 + b_0 &= \frac{pbT_2}{1 + \alpha V_2} \left(\rho + \frac{aT_2}{T_{\max}} + \frac{bV_2}{1 + \alpha V_2} \right) \left(1 - \frac{1}{1 + \alpha V_2} \right) + \frac{aI_2}{T_{\max}} \frac{pI_2}{V_2} \left(\rho + \frac{aT_2}{T_{\max}} + \frac{bV_2}{1 + \alpha V_2} \right) \\
&\quad + \frac{pbT_2}{(1 + \alpha V_2)^2} \left(\frac{bV_2}{1 + \alpha V_2} - \frac{aI_2}{T_{\max}} \right) + \frac{aT_2}{T_{\max}} \frac{pI_2}{V_2} \left(\frac{bV_2}{1 + \alpha V_2} - \frac{aI_2}{T_{\max}} \right)
\end{aligned}$$

so we need

$$(H1) \quad a_0 + b_0 > 0, \quad a_2(a_1 + b_1) - (a_0 + b_0) > 0$$

If $\tau = 0$, by the Routh–Hurwitz criterion, we have the following theorem

Theorem 1. *If (H1) is satisfied, then the infected equilibrium $E_2(T_2, I_2, V_2)$ is locally asymptotically stable.*

Now we analyze if it is possible to have a complex root with positive real part for the case $\tau > 0$, assuming (H1) satisfies, note that $\lambda = 0$ is not a root of (10) because $a_0 + b_0 > 0$. Now suppose that $\lambda = i\omega$, with $\omega > 0$, is a root of (10) so the next equation must be satisfied by ω

$$-\omega^3 i - a_2\omega^2 + a_1\omega i + a_0 + (b_1\omega i + b_0)(\cos(\omega\tau) + \sin(\omega\tau)i) = 0.$$

Separating again the real and imaginary parts, we have the following system

$$\begin{aligned}
a_2^2\omega^2 + a_0 &= -b_0 \cos(\omega\tau) - b_1\omega \sin(\omega\tau), \\
-\omega^3 + a_1\omega &= -b_1 \cos(\omega\tau) + b_0 \sin(\omega\tau).
\end{aligned} \tag{11}$$

Now, we square both sides of each equation above and add the resulting equations, to obtain the following sixth degree equation for ω

$$\omega^6 + (a_2 - 2a_1)\omega^4 + (a_1^2 - 2a_2a_0 - b_1^2)\omega^2 + a_0^2 - b_0^2 = 0. \tag{12}$$

Let

$$z = \omega^2, \quad A = a_2 - 2a_1, \quad B = a_1^2 - 2a_2a_0 - b_1^2, \quad C = a_0^2 - b_0^2$$

then equation (12) becomes the third order equation in z

$$z^3 + Az^2 + Bz + C = 0. \quad (13)$$

Suppose that (13) at least a positive root, let z_0 the small value for this roots. Then equation (12) has the root $\omega_0 = \sqrt{z_0}$ then form (11) obtain the value of τ associated with this ω_0 such that $\lambda = \omega i$ is an purely imaginary root of (10)

$$\tau_0 = \frac{1}{\omega_0} \arccos \left[\frac{b_0(a_2\omega_0^2 - a_0) + b_1\omega_0(\omega_0^3 - a_1\omega_0)}{b_0^2 + b_1^2\omega_0^2} \right]$$

Then we have the following result, from lemma 2.1 from Ruan [20]

Theorem 2. *Suppose (H1) hold.*

- (a) *If $C \geq 0$ and $\Delta = A^2 - 3B < 0$, then all roots of equation (10) have negative real parts for all $\tau \geq 0$, then the infected equilibrium E_2 is locally asymptotically stable.*
- (b) *If $C < 0$ or $C \geq 0$, $z_1 > 0$ and $z_1^3 + Az_1^2 + Bz_1 + C \leq 0$, the all roots of equation (10) have negative real parts when $\tau \in [0, \tau_0)$, then the infected equilibrium E_2 is locally asymptotically stable in $[0, \tau_0)$.*

3.3 Global Analysis

In this section we study the global stability of the equilibria, the method to prove is to construct a Lyapunov functional

Theorem 3. *The infection-free equilibrium $E_1(T_0, 0, 0)$, with T_0 defined in (3), of system (1) is globally asymptotically stable if $R_0 \leq 1$.*

Proof. Define the Lyapunov functional

$$U(t) = \int_{T_0}^T \frac{\sigma - T_0}{\sigma} d\sigma + I + \frac{bT_0}{c}V + b \int_0^\tau \frac{T(t-\omega)V(t-\omega)}{1 + \alpha V(t-\omega)} d\omega$$

U is defined and is continuous for any positive solution $(T(t), I(t), V(t))$ of system (1) and $U = 0$ at $E_1(T_0, 0, 0)$. And calculating the derivative of $U(t)$ along positive solutions of (1), it follows that

$$\begin{aligned} \frac{dU}{dt} &= \frac{T - T_0}{T} \dot{T}(t) + \dot{I}(t) + \frac{bT_0}{c} \dot{V} - b \int_0^\tau \frac{d}{d\omega} \frac{T(t-\omega)V(t-\omega)}{1 + \alpha V(t-\omega)} d\omega \\ &= \frac{T - T_0}{T} \left(s - dT + aT \left(1 - \frac{T + I}{T_{\max}} \right) - \frac{bTV}{1 + \alpha V} \right) + \frac{bT(t-\tau)V(t-\tau)}{1 + \alpha V(t-\tau)} - \mu I \\ &\quad + aI \left(1 - \frac{I + T}{T_{\max}} \right) + \frac{bT_0}{c} (pI - cV) - \frac{bT(t-\tau)V(t-\tau)}{1 + \alpha V(t-\tau)} + \frac{bTV}{1 + \alpha V} \\ &= (T - T_0) \left(\frac{s}{T} - d + a \left(1 - \frac{T + I}{T_{\max}} \right) - \frac{bV}{1 + \alpha V} \right) - \mu I + aI \left(1 - \frac{I + T}{T_{\max}} \right) \\ &\quad + \frac{bT_0}{c} (pI - cV) + \frac{bTV}{1 + \alpha V} \end{aligned}$$

using $a - d = \frac{aT_0}{T_{\max}} - \frac{s}{T_0}$ and simplifying, we get

$$\begin{aligned}
\frac{dU}{dt} &= (T - T_0) \left(-s \left(\frac{T - T_0}{TT_0} \right) - \frac{a}{T_{\max}}(T - T_0) - \frac{aI}{T_{\max}} - \frac{bV}{1 + \alpha V} \right) - \mu I + aI \left(1 - \frac{I + T}{T_{\max}} \right) \\
&\quad + \frac{bT_0}{c}(pI - cV) + \frac{bTV}{1 + \alpha V} \\
&= -s \frac{(T - T_0)^2}{TT_0} - \frac{a}{T_{\max}}(T - T_0)^2 - \frac{a}{T_{\max}}I(T - T_0) - \frac{b(T - T_0)V}{1 + \alpha V} - \mu I + aI - \frac{a}{T_{\max}}IT \\
&\quad - \frac{a}{T_{\max}}I^2 + \frac{bpT_0}{c}I - bT_0V + \frac{bTV}{1 + \alpha V} \\
&\leq -s \frac{(T - T_0)^2}{TT_0} - \frac{a}{T_{\max}}(T - T_0)^2 - \frac{a}{T_{\max}}I(T - T_0) - \frac{b(T - T_0)V}{1 + \alpha V} - \mu I + aI - \frac{a}{T_{\max}}IT \\
&\quad - \frac{a}{T_{\max}}I^2 + \frac{bpT_0}{c}I - \frac{bT_0V}{1 + \alpha V} + \frac{bTV}{1 + \alpha V} + \frac{a}{T_{\max}}IT_0 - \frac{a}{T_{\max}}IT_0 \\
&= -s \frac{(T - T_0)^2}{TT_0} - \frac{a}{T_{\max}}(T - T_0)^2 - \frac{2a}{T_{\max}}I(T - T_0) - \mu I + aI - \frac{a}{T_{\max}}I^2 + \frac{bpT_0}{c}I \\
&\quad - \frac{a}{T_{\max}}IT_0 \\
&= -s \frac{(T - T_0)^2}{TT_0} - \frac{a}{T_{\max}}[(T - T_0) + I]^2 + I \left(a \left(1 - \frac{T_0}{T_{\max}} \right) + \frac{bT_0p}{c} - \mu \right)
\end{aligned}$$

note that

$$a \left(1 - \frac{T_0}{T_{\max}} \right) + \frac{bT_0p}{c} - \mu = \mu(R_0 - 1) \leq 0,$$

since $R_0 \leq 1$, therefore

$$\dot{L}(t) \leq - \left(s \frac{(T - T_0)^2}{TT_0} + \frac{a}{T_{\max}}[(T - T_0)^2 + I] + \mu(1 - R_0)I \right) < 0$$

If $R_0 \leq 1$ then $\frac{dU}{dt} \leq 0$ from corollary 5.2 in [12], E_1 is globally asymptotically stable. Also, for $R_0 = 1$, $\frac{dU}{dt}(t) = 0$ if and only if $T(t) = T_0$ and $I(t) = 0$ while in the case $R_0 < 1$, $\frac{dU}{dt}(t) = 0$ if and only if $T(t) = T_0$ and $I(t) = 0$. Therefore, the largest invariant set in $\left\{ (T(t), I(t), V(t)) : \frac{dU}{dt} = 0 \right\}$ when $R_0 \leq 1$ is $E_1(T_0, 0, 0)$. By the classical Lyapunov-LaSalle invariance principle (theorem 5.3 in [12]), E_1 is globally asymptotically stable. \square

In the following, we consider the global asymptotic stability of a unique infected equilibrium E_2 . We construct an Lyapunov functional for infected equilibrium, using suitable combinations of the Lyapunov functions given in [11] and the Volterra-type functionals [15, 25].

Theorem 4. *If $R_0 > 1$ and $a \leq d + \frac{a}{T_{\max}}[T_2 + I_2]$, then the unique infected equilibrium E_2 of (1) is globally asymptotically stable for any $\tau \geq 0$.*

Proof. Define a Lyapunov functional for E_2 ,

$$L(t) = \tilde{L}(t) + \frac{bT_2V_2}{1 + \alpha V_2}L_+(t),$$

where

$$\tilde{L} = \int_{T_2}^T \frac{(\sigma - T_2)}{\sigma} d\sigma + \int_{I_2}^I \frac{(\sigma - I_2)}{\sigma} d\sigma + \frac{bT_2V_2}{pI_2(1 + \alpha V_2)} \int_{V_2}^V \left(1 - \frac{V_2(1 + \alpha\sigma)}{\sigma(1 + \alpha V_2)} \right) d\sigma,$$

and

$$L_+ = \int_0^\tau \left(\frac{T(t - \omega)V(t - \omega)(1 + \alpha V_2)}{T_2V_2(1 + \alpha V(t - \omega))} - 1 - \ln \frac{T(t - \omega)V(t - \omega)(1 + \alpha V_2)}{T_2V_2(1 + \alpha V(t - \omega))} \right) d\omega.$$

At infected equilibrium, we have

$$a - d = -\frac{s}{T_2} + \frac{bV_2}{1 + \alpha V_2} + \frac{a}{T_{\max}}(T_2 + I_2), \quad (14)$$

$$a - \mu = -\frac{bT_2V_2}{I_2(1 + \alpha V_2)} + \frac{a}{T_{\max}}(T_2 + I_2), \quad (15)$$

$$c = p\frac{I_2}{V_2}. \quad (16)$$

The derivative of \tilde{L} with respect to t along the solutions of (1), we get

$$\begin{aligned} \frac{d\tilde{L}}{dt} &= \frac{(T - T_2)}{T} \dot{T} + \frac{(I - I_2)}{I} \dot{I} + \frac{bT_2V_2}{pI_2(1 + \alpha V_2)} \left(1 - \frac{V_2(1 + \alpha V)}{V(1 + \alpha V_2)} \right) \dot{V}, \\ &= (T - T_2) \left(\frac{s}{T} - \frac{a}{T_{\max}}(T + I) - \frac{bV}{1 + \alpha V} + a - d \right) \\ &\quad + (I - I_2) \left(\frac{bT(t - \tau)V(t - \tau)}{I(1 + \alpha V(t - \tau))} - \frac{a}{T_{\max}}(T + I) + a - \mu \right) \\ &\quad + \frac{bT_2V_2}{pI_2(1 + \alpha V_2)} \left(1 - \frac{V_2(1 + \alpha V)}{V(1 + \alpha V_2)} \right) (pI - cV). \end{aligned}$$

Using (14)–(15) and (16), we get

$$\begin{aligned} \frac{d\tilde{L}}{dt} &= (T - T_2) \left(-s\frac{(T - T_2)}{TT_2} - \frac{a}{T_{\max}}[(T - T_2) + (I - I_2)] - b\left(\frac{V}{1 + \alpha V} - \frac{V_2}{1 + \alpha V_2}\right) \right) \\ &\quad + (I - I_2) \left(b\left(\frac{T(t - \tau)V(t - \tau)}{I(1 + \alpha V(t - \tau))} - \frac{T_2V_2}{I_2(1 + \alpha V_2)}\right) - \frac{a}{T_{\max}}[(T - T_2) + (I - I_2)] \right) \\ &\quad + \frac{bT_2V_2}{pI_2(1 + \alpha V_2)} \left(1 - \frac{V_2(1 + \alpha V)}{V(1 + \alpha V_2)} \right) \left(pI - pI_2\frac{V}{V_2} \right). \end{aligned}$$

Cancelling identical terms with opposite signs and collecting terms, yields

$$\begin{aligned} \frac{d\tilde{L}}{dt} &= -s\frac{(T - T_2)^2}{TT_2} - \frac{a}{T_{\max}}[(T - T_2) + (I - I_2)]^2 \\ &\quad + \frac{bT_2V_2}{1 + \alpha V_2} \left(-\frac{TV(1 + \alpha V_2)}{T_2V_2(1 + \alpha V)} + \frac{T(t - \tau)V(t - \tau)(1 + \alpha V_2)}{T_2V_2(1 + \alpha V(t - \tau))} \right) \\ &\quad + \frac{bT_2V_2}{1 + \alpha V_2} \left(-\frac{IV_2(1 + \alpha V)}{I_2V(1 + \alpha V_2)} - \frac{T(t - \tau)I_2V(t - \tau)(1 + \alpha V_2)}{T_2IV_2(1 + \alpha V(t - \tau))} \right) \\ &\quad + \frac{bT_2V_2}{1 + \alpha V_2} \left(\frac{T}{T_2} + \frac{V(1 + \alpha V_2)}{V_2(1 + \alpha V)} - \frac{V}{V_2} + \frac{(1 + \alpha V)}{(1 + \alpha V_2)} \right). \end{aligned}$$

We can rewrite $\frac{d\tilde{L}}{dt}$ as

$$\begin{aligned}\frac{d\tilde{L}}{dt} = & -s \frac{(T - T_2)^2}{TT_2} - \frac{a}{T_{\max}} [(T - T_2) + (I - I_2)]^2 \\ & + \frac{bT_2V_2}{1 + \alpha V_2} \left(-\frac{TV(1 + \alpha V_2)}{T_2V_2(1 + \alpha V)} + \frac{T(t - \tau)V(t - \tau)(1 + \alpha V_2)}{T_2V_2(1 + \alpha V(t - \tau))} \right) \\ & + \frac{bT_2V_2}{1 + \alpha V_2} \left(3 - \frac{T_2}{T} - \frac{IV_2(1 + \alpha V)}{I_2V(1 + \alpha V_2)} - \frac{T(t - \tau)I_2V(t - \tau)(1 + \alpha V_2)}{T_2IV_2(1 + \alpha V(t - \tau))} \right) \\ & + \frac{bT_2V_2}{1 + \alpha V_2} \left(\frac{V(1 + \alpha V_2)}{V_2(1 + \alpha V)} - \frac{V}{V_2} + \frac{(1 + \alpha V)}{(1 + \alpha V_2)} - 1 \right) + \frac{bT_2V_2}{1 + \alpha V_2} \left(\frac{T_2}{T} + \frac{T}{T_2} - 2 \right),\end{aligned}$$

replacing the term $\frac{T}{T_2} + \frac{T_2}{T} - 2$ by $\frac{(T - T_2)^2}{T_2}$,

$$\begin{aligned}\frac{d\tilde{L}}{dt} = & - \left(s - \frac{bT_2V_2}{1 + \alpha V_2} \right) \frac{(T - T_2)^2}{TT_2} - \frac{a}{T_{\max}} [(T - T_2) + (I - I_2)]^2 \\ & + \frac{bT_2V_2}{1 + \alpha V_2} \left(-\frac{TV(1 + \alpha V_2)}{T_2V_2(1 + \alpha V)} + \frac{T(t - \tau)V(t - \tau)(1 + \alpha V_2)}{T_2V_2(1 + \alpha V(t - \tau))} \right) \\ & + \frac{bT_2V_2}{1 + \alpha V_2} \left(3 - \frac{T_2}{T} - \frac{IV_2(1 + \alpha V)}{I_2V(1 + \alpha V_2)} - \frac{T(t - \tau)I_2V(t - \tau)(1 + \alpha V_2)}{T_2IV_2(1 + \alpha V(t - \tau))} \right) \\ & + \frac{bT_2V_2}{1 + \alpha V_2} \left(1 - \frac{V_2(1 + \alpha V)}{V(1 + \alpha V_2)} \right) \left(\frac{V(1 + \alpha V_2)}{V_2(1 + \alpha V)} - \frac{V}{V_2} \right).\end{aligned}$$

Using $s - \frac{bT_2V_2}{1 + \alpha V_2} = (d - a)T_2 + \frac{aT_2}{T_{\max}}[T_2 + I_2]$, we get

$$\begin{aligned}\frac{d\tilde{L}}{dt} = & - \left(d - a + \frac{a}{T_{\max}}[T_2 + I_2] \right) \frac{(T - T_2)^2}{T} - \frac{a}{T_{\max}} [(T - T_2) + (I - I_2)]^2 \\ & + \frac{bT_2V_2}{1 + \alpha V_2} \left(-\frac{TV(1 + \alpha V_2)}{T_2V_2(1 + \alpha V)} + \frac{T(t - \tau)V(t - \tau)(1 + \alpha V_2)}{T_2V_2(1 + \alpha V(t - \tau))} \right) \\ & + \frac{bT_2V_2}{1 + \alpha V_2} \left(3 - \frac{T_2}{T} - \frac{IV_2(1 + \alpha V)}{I_2V(1 + \alpha V_2)} - \frac{T(t - \tau)I_2V(t - \tau)(1 + \alpha V_2)}{T_2IV_2(1 + \alpha V(t - \tau))} \right) \\ & - \alpha bT_2 \frac{(V - V_2)^2}{(1 + \alpha V)(1 + \alpha V_2)^2}.\end{aligned}$$

It is easy to see that

$$\begin{aligned}
\frac{dL_+}{dt} &= \frac{d}{dt} \int_0^\tau \left(\frac{T(t-\omega)V(t-\omega)(1+\alpha V_2)}{T_2V_2(1+\alpha V(t-\omega))} - 1 - \ln \frac{T(t-\omega)V(t-\omega)(1+\alpha V_2)}{T_2V_2(1+\alpha V(t-\omega))} \right) d\omega, \\
&= \int_0^\tau \frac{d}{dt} \left(\frac{T(t-\omega)V(t-\omega)(1+\alpha V_2)}{T_2V_2(1+\alpha V(t-\omega))} - 1 - \ln \frac{T(t-\omega)V(t-\omega)(1+\alpha V_2)}{T_2V_2(1+\alpha V(t-\omega))} \right) d\omega, \\
&= - \int_0^\tau \frac{d}{d\omega} \left(\frac{T(t-\omega)V(t-\omega)(1+\alpha V_2)}{T_2V_2(1+\alpha V(t-\omega))} - 1 - \ln \frac{T(t-\omega)V(t-\omega)(1+\alpha V_2)}{T_2V_2(1+\alpha V(t-\omega))} \right) d\omega, \\
&= - \left[\frac{T(t-\omega)V(t-\omega)(1+\alpha V_2)}{T_2V_2(1+\alpha V(t-\omega))} - 1 - \ln \frac{T(t-\omega)V(t-\omega)(1+\alpha V_2)}{T_2V_2(1+\alpha V(t-\omega))} \right]_{\omega=0}^\tau, \\
&= - \frac{T(t-\tau)V(t-\tau)(1+\alpha V_2)}{T_2V_2(1+\alpha V(t-\tau))} + \frac{TV(1+\alpha V_2)}{T_2V_2(1+\alpha V)} + \ln \frac{T(t-\tau)V(t-\tau)(1+\alpha V_2)}{T_2V_2(1+\alpha V(t-\tau))} \\
&\quad + \ln \frac{T_2V_2(1+\alpha V)}{TV(1+\alpha V_2)}, \\
&= - \frac{T(t-\tau)V(t-\tau)(1+\alpha V_2)}{T_2V_2(1+\alpha V(t-\tau))} + \frac{TV(1+\alpha V_2)}{T_2V_2(1+\alpha V)} + \ln \frac{T(t-\tau)I_2V(t-\tau)(1+\alpha V_2)}{T_2IV_2(1+\alpha V(t-\tau))} \\
&\quad + \ln \frac{T_2}{T} + \ln \frac{IV_2(1+\alpha V)}{I_2V(1+\alpha V_2)}.
\end{aligned}$$

Since

$$\frac{dL}{dt} = \frac{d\tilde{L}}{dt} + \frac{bT_2V_2}{1+\alpha V_2} \frac{dL_+}{dt},$$

we obtain

$$\begin{aligned}
\frac{dL}{dt} &= - \left(d - a + \frac{a}{T_{\max}}[T_2 + I_2] \right) \frac{(T - T_2)^2}{T} - \frac{a}{T_{\max}}[(T - T_2) + (I - I_2)]^2 \\
&\quad - \frac{bT_2V_2}{1+\alpha V_2} \left(\frac{T_2}{T} - 1 - \ln \frac{T_2}{T} \right) - \frac{bT_2V_2}{1+\alpha V_2} \left(\frac{IV_2(1+\alpha V)}{I_2V(1+\alpha V_2)} - 1 - \ln \frac{IV_2(1+\alpha V)}{I_2V(1+\alpha V_2)} \right) \\
&\quad - \frac{bT_2V_2}{1+\alpha V_2} \left(\frac{T(t-\tau)I_2V(t-\tau)(1+\alpha V_2)}{T_2IV_2(1+\alpha V(t-\tau))} - 1 - \ln \frac{T(t-\tau)I_2V(t-\tau)(1+\alpha V_2)}{T_2IV_2(1+\alpha V(t-\tau))} \right) \\
&\quad - \alpha bT_2 \frac{(V - V_2)^2}{(1+\alpha V)(1+\alpha V_2)^2}.
\end{aligned}$$

Thus, $a \leq d + \frac{a}{T_{\max}}[T_2 + I_2]$ implies that $dL/dt \leq 0$. By Corollary 5.2 in [12], solutions limit to \mathbb{M} , the largest invariant subset of $\{dL/dt = 0\}$. Furthermore, $dL/dt = 0$ if and only if $T(t) = T(t-\tau) = T_2$, $V(t) = V(t-\tau) = V_2$ and $I(t) = I_2$. Therefore the largest compact invariant set in \mathbb{M} is the singleton $\{E_2\}$, where E_2 is the infected equilibrium. This shows that $\lim_{t \rightarrow \infty} (T(t), I(t), V(t)) = (T_2, I_2, V_2)$. By the classical Lyapunov-LaSalle invariance principle (Theorem 5.3 in [12]), if $a \leq d + \frac{a}{T_{\max}}[T_2 + I_2]$ then E_2 is globally asymptotically stable. This proves Theorem 4. \square

As is well known, the Lyapunov functions are never unique. We constructed a Volterra-type Lyapunov functional for the infected equilibrium to prove Theorem 4

$$L(t) = \hat{L}(t) + \frac{bT_2V_2}{1+\alpha V_2} L_+(t),$$

where

$$\hat{L} = \int_{T_2}^T \frac{(\sigma - T_2)}{\sigma} d\sigma + \int_{I_2}^I \frac{(\sigma - I_2)}{\sigma} d\sigma + \frac{bT_2V_2}{pI_2(1 + \alpha V_2)} \int_{V_2}^V \left(1 - \frac{V_2}{\sigma}\right) d\sigma.$$

The time derivative of $L(t)$ computed along solutions of (1), is given by the expression

$$\begin{aligned} \frac{dL}{dt} = & - \left(d - a + \frac{a}{T_{\max}}[T_2 + I_2] \right) \frac{(T - T_2)^2}{T} - \frac{a}{T_{\max}}[(T - T_2) + (I - I_2)]^2 \\ & - \frac{bT_2V_2}{1 + \alpha V_2} \left(\frac{T_2}{T} - 1 - \ln \frac{T_2}{T} \right) - \frac{bT_2V_2}{1 + \alpha V_2} \left(\frac{IV_2}{I_2V} - 1 - \ln \frac{IV_2}{I_2V} \right) \\ & - \frac{bT_2V_2}{1 + \alpha V_2} \left(\frac{T(t - \tau)I_2V(t - \tau)(1 + \alpha V_2)}{T_2IV_2(1 + \alpha V(t - \tau))} - 1 - \ln \frac{T(t - \tau)I_2V(t - \tau)(1 + \alpha V_2)}{T_2IV_2(1 + \alpha V(t - \tau))} \right) \\ & - \frac{bT_2V_2}{1 + \alpha V_2} \left(\frac{1 + \alpha V}{1 + \alpha V_2} - 1 - \ln \frac{1 + \alpha V}{1 + \alpha V_2} \right) - \alpha bT_2 \frac{(V - V_2)^2}{(1 + \alpha V)(1 + \alpha V_2)^2}. \end{aligned}$$

4 Hopf Bifurcation Analysis

For the bifurcation analysis we use the delay τ as a bifurcation parameter to find an interval in which the infected equilibria is stable and unstable out of the same margins. Now to establish the Hopf bifurcation at $\tau = \tau_0$ we need to show that $\frac{d\text{Re}\lambda(\tau_0)}{d\tau} > 0$ differentiating (10) with respect to τ we get

$$\frac{d\lambda}{d\tau} = \frac{\lambda(b_1\lambda + b_0)e^{-\lambda\tau}}{3\lambda^2 + 2a_2\lambda + a_1 + b_1e^{-\lambda\tau} - (b_1\lambda + b_0)e^{-\lambda\tau}}$$

this gives

$$\begin{aligned} \left(\frac{d\lambda}{d\tau} \right)^{-1} &= \frac{3\lambda^2 + 2a_2\lambda + a_1 + b_1e^{-\lambda\tau} - (b_1\lambda + b_0)e^{-\lambda\tau}}{\lambda(b_1\lambda + b_0)e^{-\lambda\tau}} \\ &= \frac{3\lambda^2 + 2a_2\lambda + a_1 + b_1e^{-\lambda\tau}}{\lambda(b_1\lambda + b_0)e^{-\lambda\tau}} - \frac{\tau}{\lambda} \\ &= \frac{3\lambda^3 + 2a_2\lambda^2 + a_1\lambda + b_1\lambda e^{-\lambda\tau}}{\lambda^2(b_1\lambda + b_0)e^{-\lambda\tau}} - \frac{\tau}{\lambda} \\ \left(\frac{d\lambda}{d\tau} \right)^{-1} &= \frac{2\lambda^3 + a_2\lambda^2 - a_0 - b_0e^{-\lambda\tau}}{\lambda^2(b_1\lambda + b_0)e^{-\lambda\tau}} - \frac{\tau}{\lambda} \\ &= - \frac{2\lambda^3 + a_2\lambda^2 - a_0}{\lambda^2(\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0)} - \frac{b_0}{\lambda^2(b_1\lambda + b_0)} - \frac{\tau}{\lambda} \end{aligned}$$

It is important to be aware that we used (10) in several equalities. Thus,

$$\begin{aligned}
\text{sign} \left\{ \frac{d\text{Re}\lambda}{d\tau} \right\}_{\lambda=i\omega_0} &= \text{sign} \left\{ \text{Re} \left(\frac{d\lambda}{d\tau} \right) \right\}_{\lambda=i\omega_0} \\
&= \text{sign} \left\{ \text{Re} \left[-\frac{2\lambda^3 + a_2\lambda^2 - a_0}{\lambda^2(\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0)} - \frac{b_0}{\lambda^2(b_1\lambda + b_0)} - \frac{\tau}{\lambda} \right]_{\lambda=i\omega_0} \right\} \\
&= \text{sign} \left\{ \text{Re} \left[-\frac{-2\omega_0^3 i - a_2\omega_0^2 i - a_0}{-\omega_0^2(-\omega_0^3 i - a_2\omega_0^2 + a_1\omega_0 i + a_0)} - \frac{b_0}{-\omega_0^2(b_1\omega_0 i + b_0)} - \frac{\tau_0}{\omega_0 i} \right] \right\} \\
&= \text{sign} \left\{ \frac{2\omega_0^6 + (a_2^2 - 2a_1)\omega_0^4 - a_0^2}{\omega_0^2[(a_2\omega_0^2 - a_0)^2 + (\omega_0^3 - a_1\omega_0)^2]} + \frac{b_0^2}{\omega_0^2[b_0^2 + (b_1\omega_0)^2]} \right\} \\
&= \text{sign} \left\{ \frac{2\omega_0^6 + (a_2^2 - 2a_1)\omega_0^4 + b_0^2 - a_0^2}{\omega_0^2[(a_2\omega_0^2 - a_0)^2 + (\omega_0^3 - a_1\omega_0)^2]} \right\} \\
&= \text{sign} \left\{ \frac{2\omega_0^6 + (a_2^2 - 2a_1)\omega_0^4 + (\omega_0^3 - a_1\omega_0)^2 + (a_1^2 - 2a_0a_2 - b_1^2)\omega_0^2}{\omega_0^2[(a_2\omega_0^2 - a_0)^2 + (\omega_0^3 - a_1\omega_0)^2]} \right\} \\
&= \text{sign} \left\{ \frac{3\omega_0^4 + 2(a_2^2 - 2a_1)\omega_0^2 + a_1^2 - 2a_0a_2 - b_1^2}{(a_2\omega_0^2 - a_0)^2 + (\omega_0^3 - a_1\omega_0)^2} \right\}.
\end{aligned}$$

It is also important to notice that we used (10)-(12) in several equalities. Now to conclude that $\frac{d\text{Re}\lambda}{d\tau} > 0$ consider the next lemma

Lemma 2 ([28]). *Supposed that x_1, x_2, x_3 are the roots of equation $g(x) = x^3 + \alpha x^2 + \beta x + \gamma = 0$ ($\beta < 0$), and x_3 is the largest positive simple root, then*

$$\left. \frac{dg(x)}{dx} \right|_{x=x_3} > 0.$$

In our case, considering $F(z) = z^3 + Az^2 + Bz + C = 0$, defined in (13), and assuming $B < 0$ and ω_0^2 as the largest positive root we have

$$\frac{d\text{Re}\lambda}{d\tau} = \frac{\frac{dF(z)}{dz}}{(a_2\omega_0^2 - a_0)^2 + (\omega_0^3 - a_1\omega_0)^2} > 0.$$

The above analysis can be summarized into the following theorem:

Theorem 5. *Suppose that*

(i) $R_0 > 1$.

If either

(ii) $C < 0$

or

(iii) $C \geq 0$ and $B < 0$

is satisfied, and ω_0 is the largest positive simple root of (13) then the infected equilibrium E_2 of model (1) is locally asymptotically stable when $\tau < \tau_0$ and unstable when $\tau > \tau_0$ where

$$\tau_0 = \frac{1}{\omega_0} \arccos \left[\frac{b_0(a_2\omega_0^2 - a_0) + b_1\omega_0(\omega_0^3 - a_1\omega_0)}{b_0^2 + b_1^2\omega_0^2} \right]$$

when $\tau = \tau_0$, a Hopf bifurcation occurs; that is a family of periodic solutions bifurcates from E_2 as τ passes through the critical value τ_0 .

5 Permanence

Lemma 3. *For any solution $(T(t), I(t), V(t))$ of system (1), we have*

$$\limsup_{t \rightarrow \infty} T(t) \leq T_0 = \frac{T_{\max}}{2a} \left[a - d + \sqrt{(a - d)^2 + \frac{4as}{T_{\max}}} \right].$$

Then there is a $t_1 > 0$ such that for any sufficiently small $\epsilon > 0$, we have $T(t) \leq T_0 + \epsilon$ for $t > t_1$.

The previous lemma follows, noting that for the first equation of (1), we have

$$\dot{T}(t) \leq s - (d - a)T(t) - \frac{a}{T_{\max}}T^2(t)$$

Theorem 6. *There exist $M_I, M_V > 0$ such that for any positive solution $(T(t), I(t), V(t))$ of system (1),*

$$I(t) < M_I, \quad V(t) < M_V$$

for all large t .

Proof. Let $W(t) = T(t - \tau) + I(t)$, then

$$\begin{aligned} \dot{W}(t) &= \dot{T}(t - \tau) + \dot{I}(t) \\ &= s - dT(t - \tau) + aT(t - \tau) \left(1 - \frac{T(t - \tau) + I(t - \tau)}{T_{\max}} \right) - \frac{bT(t - \tau)V(t - \tau)}{1 + \alpha V(t - \tau)} + \\ &\quad \frac{bT(t - \tau)V(t - \tau)}{1 + \alpha V(t - \tau)} - \mu I + aI \left(1 - \frac{T + I}{T_{\max}} \right) \\ &= s - dT(t - \tau) + aT(t - \tau) \left(1 - \frac{T(t - \tau) + I(t - \tau)}{T_{\max}} \right) - \mu I + aI \left(1 - \frac{T + I}{T_{\max}} \right) \\ &= s - dT(t - \tau) + aT(t - \tau) - \frac{aT^2(t - \tau)}{T_{\max}} - \frac{aT(t - \tau)I(t - \tau)}{T_{\max}} - \mu I + aI - \frac{aTI}{T_{\max}} \\ &\quad - \frac{aI^2}{T_{\max}}. \end{aligned}$$

Using that, $-\frac{a}{T_{\max}}(T(t - \tau) - \frac{T_{\max}}{2})^2 + \frac{aT_{\max}}{4} = -\frac{aT^2(t - \tau)}{T_{\max}} + aT(t - \tau)$ and $-\frac{a}{T_{\max}}(I - \frac{T_{\max}}{2})^2 + \frac{aT_{\max}}{4} = -\frac{aI^2}{T_{\max}} + aI$, we get

$$\begin{aligned} \dot{W}(t) &= s - dT(t - \tau) - \frac{a}{T_{\max}} \left(T(t - \tau) - \frac{T_{\max}}{2} \right)^2 - \frac{a}{T_{\max}} \left(I - \frac{T_{\max}}{2} \right)^2 + \frac{aT_{\max}}{2} + \\ &\quad - \frac{aT(t - \tau)I(t - \tau)}{T_{\max}} - \mu I - \frac{aTI}{T_{\max}}, \end{aligned}$$

then

$$\begin{aligned} \dot{W}(t) &= -dT(t - \tau) - \mu I - \frac{a}{T_{\max}} \left(T(t - \tau) - \frac{T_{\max}}{2} \right)^2 - \frac{a}{T_{\max}} \left(I - \frac{T_{\max}}{2} \right)^2 + \frac{aT_{\max} + 2s}{2} + \\ &\quad - \frac{aT(t - \tau)I(t - \tau)}{T_{\max}} - \frac{aTI}{T_{\max}} \\ &\leq -dT(t - \tau) - \mu I(t) + \frac{aT_{\max} + 2s}{2}, \end{aligned}$$

therefore

$$\dot{W}(t) \leq -dW(t) + \frac{aT_{\max} + 2s}{2}$$

where $d \leq \mu$. Hence, we get the boundness of $W(t)$

$$\limsup_{t \rightarrow \infty} W(t) = \frac{aT_{\max}/2 + s}{h},$$

that is, there exist $t_2 > 0$ and $M_1 > 0$ such that $W(t) < M_1$ for $t > t_2$. Then $I(t)$ has an ultimately upper bound M_I .

It follows from the third equation of system (1) that $V(t)$ has an ultimately upper bound, say M_V . Then the assertion of theorem follows and the proof is complete. \square

Define

$$\Omega = \{(T, I, V) : 0 \leq T \leq T_0, 0 \leq I \leq M_I, 0 \leq V \leq M_V\}$$

System (1) satisfies, for some $t_1 > 0$,

$$\dot{T} \geq s - dT + aT \left(1 - \frac{T + M_I}{T_{\max}}\right) - \frac{bT}{\alpha}$$

which implies that

$$\liminf_{t \rightarrow \infty} T(t) \geq \frac{T_{\max}}{2a} \left[a - d - \frac{b}{\alpha} - \frac{aM_I}{T_{\max}} + \sqrt{\left(a - d - \frac{b}{\alpha} - \frac{aM_I}{T_{\max}}\right)^2 + \frac{4as}{T_{\max}}} \right]$$

Now we shall prove that the instability of E_1 implies that system (1) is permanent.

Definition 1. *System (1) is said to be uniformly persistent, if there is an $\eta > 0$ (independent of the initial data) such that every solution $(T(t), I(t), V(t))$ with initial condition of system (1) satisfies $\liminf_{t \rightarrow \infty} T(t) \geq \eta$, $\liminf_{t \rightarrow \infty} I(t) \geq \eta$, $\liminf_{t \rightarrow \infty} V(t) \geq \eta$.*

For dissipative system uniform persistence is equivalent to the permanence.

Theorem 7. *System (1) is permanent provided $R_0 > 1$.*

We present the persistence theory for infinite dimensional system from Hale [7]. Let X be a complete space metric. Suppose that $X^0 \subset X$, $X_0 \subset X$, $X^0 \cap X_0 = \emptyset$, $X = X^0 \cup X_0$. Assume that $Y(t)$ is C^0 -semigroup on X satisfying

$$\begin{cases} Y(t) : X^0 \rightarrow X^0, \\ Y(t) : X_0 \rightarrow X_0. \end{cases} \quad (17)$$

Let $Y_b(t) = Y(t)|_{X_0}$ and let A_b be the global attractor for $Y_b(t)$.

Lemma 4. *Suppose that $Y(t)$ satisfies (17) and we have the following:*

1. *there is a $t_0 \geq 0$ such that $Y(t)$ is compact for $t > t_0$,*
2. *$Y(t)$ is a point dissipative in X ,*
3. *$\bar{A}_b = \cup_{x \in A_b} \omega(x)$ is isolated and has an acyclic covering \bar{M} , where $\bar{M} = \{M_1, M_2, \dots, M_n\}$,*
4. *$W^s(M_i) \cap X^0 = \emptyset$, for $i = 1, 2, \dots, n$.*

Then X_0 is a uniform repeller with respect to X^0 , i.e., there is an $\epsilon > 0$ such that for any $x \in X^0$

$$\liminf_{t \rightarrow \infty} d(Y(t)x, X_0) \geq \epsilon$$

, where d is the distance of $Y(t)x$ from X_0 .

We now prove theorem 7.

Proof of Theorem 7. We begin by showing that the boundary planes of \mathbb{R}_+^3 repel the positive solutions of system (1) uniformly. Let us define

$$C_0 = \{(\psi, \phi_1, \phi_2) \in C([-\tau, 0], \mathbb{R}_+^3) : \psi(\theta) \neq 0, \phi_1(\theta) = \phi_2(\theta) = 0, (\theta \in [-\tau, 0])\}.$$

If $C^0 = \text{int}C([-\tau, 0], \mathbb{R}_+^3)$, it suffices to show that there exist an ϵ_0 such that any solution u_t of system (1) initiating from C^0 , $\liminf_{t \rightarrow +\infty} d(u_t, C_0) \geq \epsilon_0$. To this end, we verify below that the conditions of lemma 4 are satisfied. It is easy to see that C^0 and C_0 are positively invariant. Moreover, conditions (1) and (2) of lemma 4 are satisfied. Thus, we only need to verify the conditions (3) and (4). There is a constant solution E_1 in C_0 , to $T(t) = T_0$, $I(t) = V(t) = 0$. If $(T(t), I(t), V(t))$ is a solution of system (1) initiating from C_0 , then $T(t) \rightarrow T_0$, $I(t) \rightarrow 0$, $V(t) \rightarrow 0$, as $t \rightarrow +\infty$. It is obvious that E_1 is an isolated invariant. Now, we show that $W^s(E_1) \cap C^0 = \emptyset$. Assuming the contrary, then there exist a positive solution $(\tilde{T}(t), \tilde{I}(t), \tilde{V}(t))$ of system (1) such that $((\tilde{T}(t), \tilde{I}(t), \tilde{V}(t))) \rightarrow (T_0, 0, 0)$ as $t \rightarrow \infty$. Let us choose $\epsilon > 0$ small enough and $t_0 > 0$ sufficiently large such that

$$T_0 - \epsilon < \tilde{T}(t) < T_0 + \epsilon, \quad 0 < \tilde{I}(t) < \epsilon$$

for $t > t_0 - \tau$. Then we have for $t > t_0$

$$\begin{cases} \dot{\tilde{I}}(t) \geq b(T_0 - \epsilon)\tilde{V}(t - \tau) + \left(-\mu + a \left(1 - \frac{T_0 + \epsilon + \epsilon}{T_{\max}}\right)\right) \tilde{I}(t), \\ \dot{\tilde{V}}(t) = p\tilde{I}(t) - c\tilde{V}(t) \end{cases}$$

Let us consider the matrix defined by

$$A_\epsilon = \begin{pmatrix} -\mu + a \left(1 - \frac{T_0 + \epsilon + \epsilon}{T_{\max}}\right) & b(T_0 - \epsilon) \\ p & -c \end{pmatrix}.$$

Since A_ϵ admits positive off-diagonal elements, Perron-Frobenius theorem implies that there is a positive eigenvector \hat{V} for the maximum eigenvalue λ_1 of A_ϵ . Moreover, since $R_0 > 1$, then $c\mu - ac \left(1 - \frac{T_0 + 2\epsilon}{T_{\max}}\right) - bp(T_0 - \epsilon) < 0$ for ϵ small enough, by a simple computation we see that λ_1 is positive.

Let us consider

$$\begin{cases} \dot{I}(t) = b(T_0 - \epsilon)V(t - \tau) + \left(-\mu + a \left(1 - \frac{T_0 + \epsilon + \epsilon}{T_{\max}}\right)\right) I(t) \\ \dot{V}(t) = pI(t) - cV(t) \end{cases} \quad (18)$$

Let $v = (v_1, v_2)$ and $l > 0$ be small enough such that

$$\begin{aligned} lv_1 &< \tilde{I}(t_0 + \theta), \\ lv_2 &< \tilde{V}(t_0 + \theta), \end{aligned}$$

for $\theta \in [-\tau, 0]$ if $(I(t), V(t))$ is a solution of system (18) satisfying $I(t) = lv_1$, $V(t) = lv_2$ for $t_0 - \tau \leq t \leq t_0$. Since the semiflow of system (18) is monotone and $A_\epsilon v > 0$, it follows that $I(t)$ and $V(t)$ are strictly increasing and $I(t) \rightarrow \infty$, $V(t) \rightarrow \infty$ as $t \rightarrow \infty$. Note that $\tilde{I} \geq I(t)$, $\tilde{V}(t) \geq V(t)$ for $t > t_0$. We have $\tilde{I}(t) \rightarrow \infty$, $\tilde{V}(t) \rightarrow \infty$ as $t \rightarrow \infty$. At this time, we are able to conclude from theorem 6 that C_0 repels the positive solutions of system (1) uniformly. Incorporating this into lemma 4 and theorem 6, we know that the system (1) is permanent. \square

6 Estimation of the length of delay to preserve stability

Let $T(t) = T_2 + X(t)$, $I(t) = I_2 + Y(t)$, $V(t) = V_2 + Z(t)$.

We consider the linearized system (1) about the equilibrium E_2 and get

$$\begin{aligned}\frac{dX}{dt} &= \left(a - d - \frac{2aT_2}{T_{\max}} - \frac{aI_2}{T_{\max}} - \frac{bV_2}{T_{\max}} \right) X - \frac{aT_2}{T_{\max}} Y - \frac{bT_2}{(1 + \alpha V_2)^2} Z \\ \frac{dY}{dt} &= -\frac{aI_2}{T_{\max}} X + \left(a - \mu - \frac{aT_2}{T_{\max}} - \frac{2aI_2}{T_{\max}} \right) Y + \frac{bV_2}{1 + \alpha V_2} X_\tau + \frac{bT_2}{(1 + \alpha V_2)^2} Z_\tau \\ \frac{dZ}{dt} &= pY - cZ\end{aligned}\tag{19}$$

Taking Laplace transform of the system given by (19), we get

$$\begin{aligned}s\mathcal{L}[X] - X(0) &= \left(a - d - \frac{2aT_2}{T_{\max}} - \frac{aI_2}{T_{\max}} - \frac{bV_2}{1 + \alpha V_2} \right) \mathcal{L}[X] - \frac{aT_2}{T_{\max}} \mathcal{L}[Y] \\ &\quad - \frac{bT_2}{(1 + \alpha V_2)^2} \mathcal{L}[Z] \\ s\mathcal{L}[Y] - Y(0) &= -\frac{aI_2}{T_{\max}} \mathcal{L}[X] - \left(a - \mu - \frac{aT_2}{T_{\max}} - \frac{2aI_2}{T_{\max}} \right) \mathcal{L}[Y] + \frac{bV_2}{1 + \alpha V_2} \mathcal{L}[X_\tau] \\ &\quad + \frac{bT_2}{(1 + \alpha V_2)^2} \mathcal{L}[Z_\tau] \\ s\mathcal{L}[Z] - Z(0) &= p\mathcal{L}[Y] - c\mathcal{L}[Z]\end{aligned}\tag{20}$$

The expressions $\mathcal{L}[Z_\tau]$ and $\mathcal{L}[X_\tau]$ are equivalent to

$$\mathcal{L}[X_\tau] = \int_0^\infty e^{-st} X(t - \tau) dt = \int_0^\tau e^{-st} X(t - \tau) dt + \int_\tau^\infty e^{-st} X(t - \tau) dt$$

taking $t = t_1 + \tau$ we can express the last equation as

$$\begin{aligned}\mathcal{L}[X_\tau] &= \int_{-\tau}^0 e^{-s(t_1 + \tau)} X(t_1) dt_1 + \int_0^\infty e^{-s(t_1 + \tau)} X(t_1) dt_1 \\ &= e^{-s\tau} \int_{-\tau}^0 e^{-st_1} X(t_1) dt_1 + e^{-s\tau} \int_0^\infty e^{-st_1} X(t_1) dt_1 \\ &= e^{-s\tau} K_1 + e^{-s\tau} \mathcal{L}[X].\end{aligned}$$

In the same way

$$\mathcal{L}[Z_\tau] = \int_0^\infty e^{-st} Z(t - \tau) dt = \int_0^\tau e^{-st} Z(t - \tau) dt + \int_\tau^\infty e^{-st} Z(t - \tau) dt.$$

We have

$$\begin{aligned}\mathcal{L}[Z_\tau] &= \int_{-\tau}^0 e^{-s(t_1 + \tau)} Z(t_1) dt_1 + \int_0^\infty e^{-s(t_1 + \tau)} Z(t_1) dt_1 \\ &= e^{-s\tau} \int_{-\tau}^0 e^{-st_1} Z(t_1) dt_1 + e^{-s\tau} \int_0^\infty e^{-st_1} Z(t_1) dt_1 \\ &= e^{-s\tau} K_2 + e^{-s\tau} \mathcal{L}[Z].\end{aligned}$$

Replacing $\mathcal{L}[X_\tau]$ and $\mathcal{L}[Z_\tau]$ on system (20) we can clear $\mathcal{L}[X]$ and $\mathcal{L}[Z]$ and we can write

$$(A - sI) \begin{pmatrix} \mathcal{L}[X] \\ \mathcal{L}[Y] \\ \mathcal{L}[Z] \end{pmatrix} = B$$

where

$$A = \begin{pmatrix} a - d - \frac{2aT_2}{T_{\max}} - \frac{aI_2}{T_{\max}} - \frac{bV_2}{1+\alpha V_2} & -\frac{aT_2}{T_{\max}} & -\frac{bT_2}{(1+\alpha V_2)^2} \\ -\frac{aI_2}{T_{\max}} + \frac{bV_2}{1+\alpha V_2}e^{-s\tau} & a - \mu - \frac{aT_2}{T_{\max}} - \frac{2aI_2}{T_{\max}} & \frac{bV_2}{(1+\alpha V_2)^2}e^{-s\tau} \\ 0 & p & c \end{pmatrix}$$

$$B = \begin{pmatrix} X(0) \\ Y(0) + (K_1 + K_2)e^{-s\tau} \\ Z(0) \end{pmatrix}.$$

The inverse Laplace transformations of $\mathcal{L}[X]$, $\mathcal{L}[Y]$ and $\mathcal{L}[Z]$ will have terms which exponentially increase with time if $\mathcal{L}[X]$, $\mathcal{L}[Y]$ and $\mathcal{L}[Z]$ have poles with positive real parts. For E_2 to be locally asymptotically stable, a necessary and sufficient condition is that all poles of $\mathcal{L}[X]$, $\mathcal{L}[Y]$ and $\mathcal{L}[Z]$ have negative real parts. We will employ the Nyquist criteria, which states that if X is the arc length of a curve encircling the right half plane, the curve $\mathcal{L}[X]$ will encircle the origin a number of times equal to the difference between the numbers of poles and zeroes of $\mathcal{L}[X]$ in the right half plane. This criteria is applied to X , Y and Z . Let

$$F(s) = s^3 + a_2s^2 + a_1s + a_0 + (b_1s + b_0)e^{-s\tau}$$

obtained from the Laplace transform. Note that $F(s) = 0$ is the characteristic equation of system (1) on the equilibrium E^* and the zeroes are the poles of $\mathcal{L}[X]$, $\mathcal{L}[Y]$ and $\mathcal{L}[Z]$. The conditions for local asymptotic stability of E_2 are given in [24]

$$\begin{aligned} \Re[F(iv_0)] &= 0 \\ \Im[F(iv_0)] &> 0, \end{aligned} \tag{21}$$

and v_0 is the smallest positive root of the first equation of (21). In our case, (21) gives

$$-a_2v_0^2 + a_0 + b_1v_0 \sin(v_0\tau) + b_0 \cos(v_0\tau) = 0 \tag{22}$$

$$-v_0^3 + a_1v_0 + b_1v_0 \cos(v_0\tau) - b_0 \sin(v_0\tau) > 0. \tag{23}$$

If (22) and (23) are satisfied simultaneously, they are sufficient conditions to guarantee stability. We shall apply them to get an estimate on the length of delay. Our aim is to find an upper bound v^+ on v_0 , independent of τ and then to estimate τ so that (23) hold for all values of v , $0 \leq v \leq v^+$ and hence in particular $v = v_0$. We rewrite (22) as

$$a_2v_0^2 = a_0 + b_1v_0 \sin(v_0\tau) + b_0 \cos(v_0\tau). \tag{24}$$

Maximizing $a_0 + b_1v_0 \sin(v_0\tau) + b_0 \cos(v_0\tau)$ subject to

$$|\sin(v_0\tau)| \leq 1, \quad |\cos(v_0\tau)| \leq 1,$$

we obtain

$$a_2v_0^2 \leq |a_0| + |b_1|v_0 + |b_0|. \tag{25}$$

Hence, if

$$v^+ = \frac{|b_1| + \sqrt{b_1^2 + 4a_2(|a_0| + |b_0|)}}{2a_2}$$

then clearly from (25) we have $v_0 \leq v^+$.

We can rewrite (23) as

$$v_0^2 < a_1 + b_1 \cos(v_0 \tau) - \frac{a_2 b_0}{v_0} \sin(v_0 \tau). \quad (26)$$

Replacing (24) in (26) and rearranging we get

$$(b_0 - a_1 b_1)(\cos(v_0 \tau) - 1) + \left(b_1 v_0 + \frac{a_2 b_0}{v_0} \right) \sin(v_0 \tau) < a_2 a_1 - a_0 + a_1 b_1 - b_0.$$

Using the bounds

$$\left| b_1 v_0 + \frac{a_2 b_0}{v_0} \right| |\sin(v_0 \tau)| \leq \left| b_1 v^+ + \frac{a_2 b_0}{v^+} \right| (v^+ \tau) = (|b_1|(v^+)^2 + |a_2 b_0|)\tau,$$

$$|b_0 - a_1 b_1| |\cos(v_0 \tau) - 1| \leq 2 |b_0 - a_1 b_1| \sin^2\left(\frac{v_0 \tau}{2}\right) \leq \frac{|b_0 - a_1 b_1|}{2} (v^+)^2 \tau^2,$$

we obtain from (26) $K_1 \tau^2 + K_2 \tau < K_3$, where

$$K_1 = \frac{|b_0 - a_1 b_1|}{2} (v^+)^2, \quad K_2 = |b_1|(v^+)^2 + |a_2 b_0|, \quad K_3 = a_2 a_1 + a_1 b_1 - a_0 - b_2$$

thus if $K_1 \tau^2 + K_2 \tau < K_3$ holds, then the inequality (22) is satisfied. A positive root of $K_1 \tau^2 + K_2 \tau = K_3$ is given by

$$\tau_+ = \frac{1}{2K_1} (-K_2 + \sqrt{K_2^2 + 4K_1 K_3}).$$

For $0 \leq \tau \leq \tau_+$, the Nyquist criteria holds. τ_+ gives estimate for the length of delay for which stability is preserved. Here τ_+ is dependent of the system parameters. Hence we can conclude that the estimate for the delay is totally dependent on system parameters for which the equilibrium E_2 is locally asymptotically stable.

Theorem 8. *If there exist a parameter $0 \leq \tau \leq \tau_+$ such that $K_1 \tau^2 + K_2 \tau < K_3$, then τ_+ is the maximum value (length of delay) of τ for which E_2 is asymptotically stable.*

7 Numerical Simulations

To explore the behaviour of the system (1) and illustrate the stability of equilibria solutions we used, dde23 [21], based on Runge-Kutta methods. We consider the values for the parameters as in [4].

In figure 1 we illustrate the stability of E_1 with the following parameters $s = 8 \times 10^5$, $d = 4.7 \times 10^{-3}$, $\mu = 0.35$, $a = 1$, $T_{\max} = 0.7 \times 10^7$, $b = 0.6 \times 10^{-7}$, $c = 5.9$, $p = 5.4$, $\alpha = 0.001$, with this values for the parameters, $R_0 = 0.9237$ so we are under conditions of theorem 1 and 3. We show the dynamic of solutions for several values of τ and we can appreciate that the solution approximates to equilibrium with oscillations as the values of τ increases.

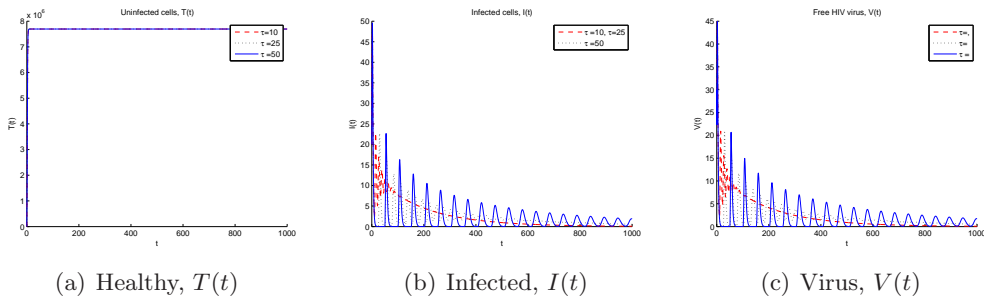


Figure 1: Stability of the E_1 equilibrium with several values of τ

In figure 2 we see the same dynamic for system (1) with a large time and different delay τ , so we can conclude that delay has no effect on stability of infection-free equilibrium for our model.

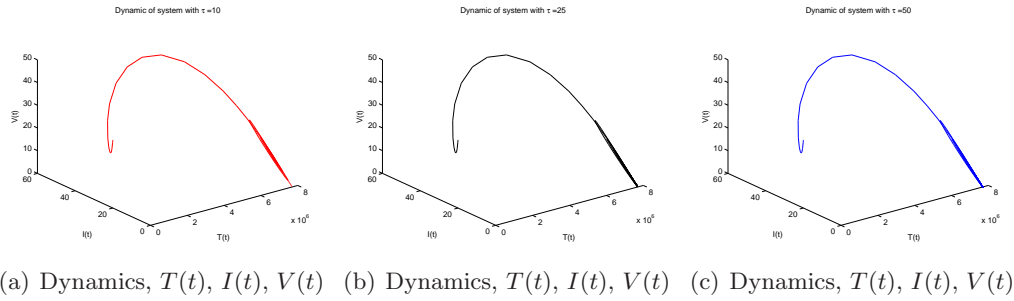


Figure 2: Phase space for different values of τ , which illustrates the stability of infection-free equilibrium E_1

For figure 3 we consider the following values for parameters $s = 8 \times 10^5$, $d = 4.7 \times 10^{-3}$, $\mu = 0.3$, $a = 2$, $T_{\max} = 0.7 \times 10^7$, $b = 0.6 \times 10^{-7}$, $c = 5.9$, $p = 5.4$ and $\alpha = 0.001$, in this case the equilibrium is $(7.363787665 \times 10^6, 1.202557883, 1.100646198)$ with $R_0 = 1.0014820$, note that this case satisfies the conditions for global stability of E_2 , as is establish in theorem 4.

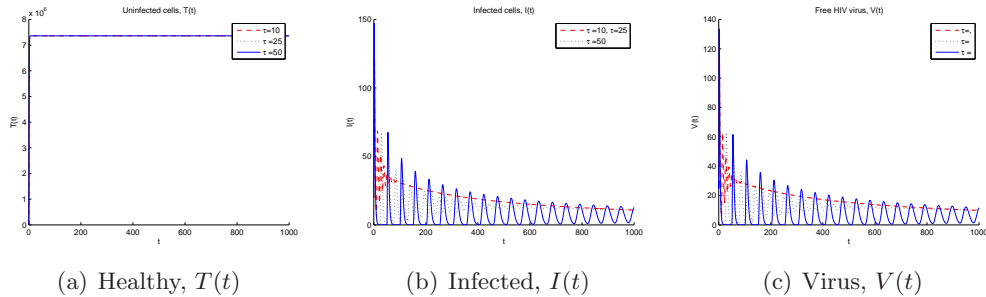


Figure 3: Stability of the infected equilibrium, E_2 , with several values of τ

In figure 4, we illustrate the the dynamic for system. (1) with respect to stability of infected equilibrium for several values of τ .

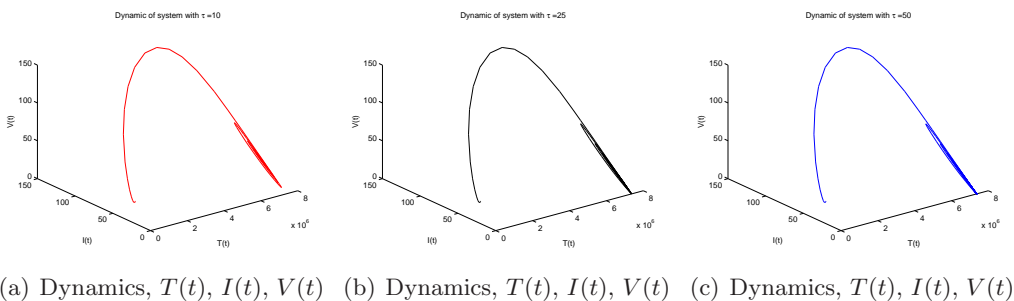


Figure 4: Phase space for different values of τ , which illustrates the stability of infection equilibrium E_2

In figures 5, 6 and 7, we illustrate the stability of E_2 according to theorem 5. In this case $s = 0.01$, $d = 0.02$, $a = 0.95$, $T_{\max} = 1200$, $b = 0.0027$, $\alpha = 0.001$, $\mu = 1$, $p = 10$, $c = 2.4$ with this values $R_0 = 13.48$, and we illustrate for different values of τ . The equilibrium is $(19.2, 106.7, 444.5)$, we can observe periodic solutions for a large value of τ , also we note that the condition for the global stability of endemic equilibrium is not satisfied.

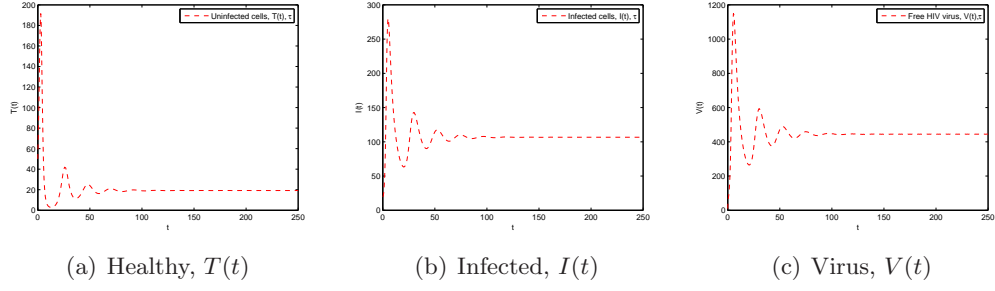


Figure 5: Stability of the E_2 equilibrium with $\tau = 0.1$

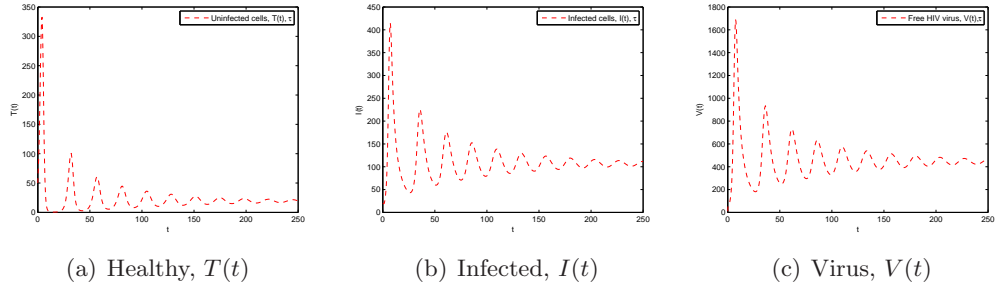


Figure 6: Stability of the E_2 equilibrium with $\tau = 1$

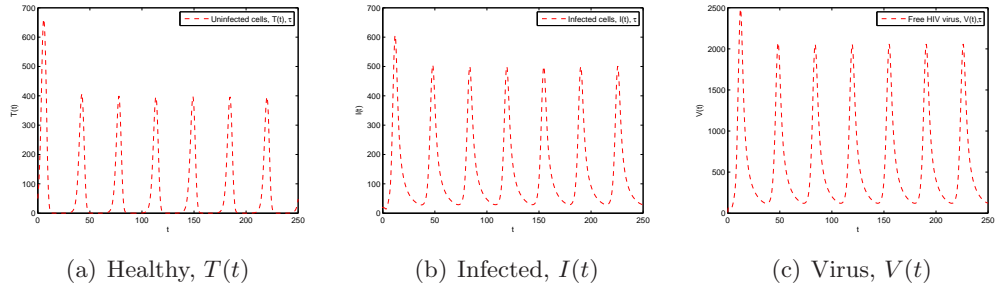
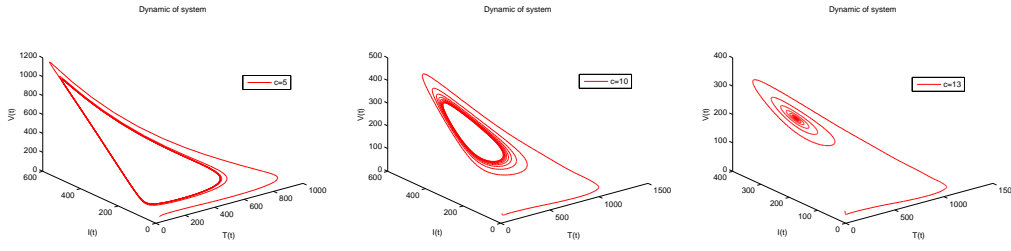


Figure 7: Stability of the E_2 equilibrium with $\tau = 3$

In figure 8 we take increasing values for c , the declination rate of virions, for the simulations we consider the values for the parameters as $s = 0.01$, $d = 0.02$, $a = 0.95$, $T_{max} = 1200$, $b = 0.0027$, $\alpha = 0.001$, $\mu = 1$, $p = 10$, and $\tau = 4$ we can observe that for a increasing value of $c = 13$ the periodic solutions have a smaller period and they disappear for c large enough

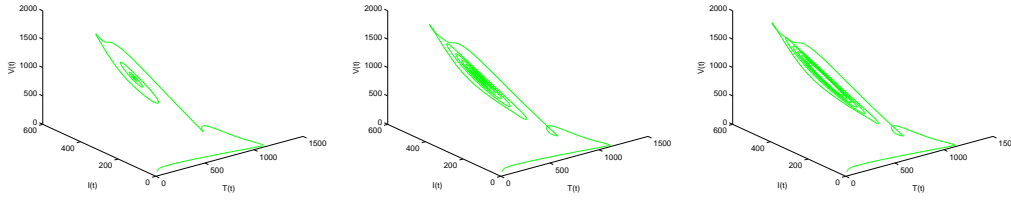


(a) Periodic solution for $c = 5$ (b) Periodic solution for $c = 10$ (c) Periodic solution for $c = 13$

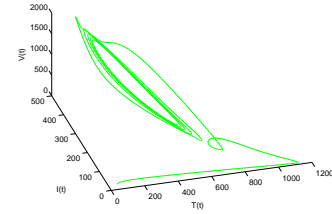
Figure 8: Periodic solutions for different values of c

The numerical simulations shows that if the clearance rate of viral particles c is sufficiently large (small) then nonexistence (existence) periodic orbits.

Now taking $\alpha = 0.005$ we can see the effect of saturation in this case the equilibrium is $(314.2, 278.7, 1161.2)$ and the dynamics for different values of τ are in figure 9, again we can observe periodic solutions for system.



(a) Dynamics, $T(t)$, $I(t)$, $V(t)$, with $\tau = 10$ (b) Dynamics, $T(t)$, $I(t)$, $V(t)$, with $\tau = 15$ (c) Dynamics, $T(t)$, $I(t)$, $V(t)$, with $\tau = 25$



(d) Dynamics, $T(t)$, $I(t)$, $V(t)$, with $\tau = 35$

Figure 9: Dynamic of system with $\alpha = 0.005$

8 Sensitivity analysis

In this section we provide a local sensitivity analysis of the basic reproduction number, in order to assess which parameter has the greatest influence on changes of R_0 values and hence the greatest effect in determining whether the disease will be cleared in the population (see e.g. [1]).

To this aim, denoting by Ψ the generic parameter of system (1), we evaluate the *normalised sensitivity index*

$$S_{\Psi} = \frac{\Psi}{R_0} \frac{\partial R_0}{\partial \Psi}$$

which indicates how sensitive R_0 is to a change of parameter Ψ . A positive (resp. negative) index indicates that an increase in the parameter value results in an increase (resp. decrease) in the R_0 value.

We consider the values $s = 0.01$, $d = 0.02$, $a = 0.95$, $T_{max} = 1200$, $b = 0.0027$, $\alpha = 0.001$, $\mu = 1$, $p = 10$, $c = 2.4$, in order to evaluate the normalised sensitivity index, we are able to show our results in figure 10, in the figure we can appreciate that the parameters b , p the infection constant rate and the reproductive rate respectively have a positive influence in the value of R_0 which means if we increase or decrease any of them by say 10% then R_0 will increase or decrease by 9.9%, note that T_{max} have the same effect. The index for parameters μ and c which represent the death rate of infected cells and the rate of clean of virions, show that increasing this values say by 10% will decrease the value of R_0 almost by a 10%. While for the parameters a , d an increase of 10% of their value will increase and decrease respectively R_0 by 2% and 1.9% and to increase s by a 100% will increase the value of R_0 by 0.8%.

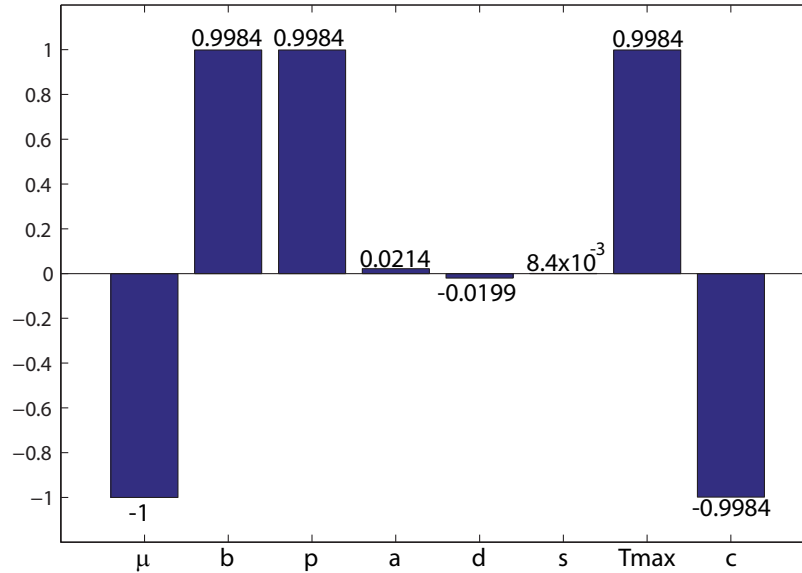


Figure 10: Sensitivity index for R_0 with respect to some chosen parameters

Other effects over R_0 can be analyzed if we consider other values for the parameters.

9 Conclusions

In this paper, we extend the hepatitis model with mitotic transmission to incorporate the effect of saturation infection function and an intracellular time delay between infection of a infected target cell and production of new virus particles.

We have established results about the local and global stability of equilibria. We can conclude than the infection-free stability is completely determined by the value of the basic reproductive number R_0 , if $R_0 \leq 1$ then the infection-free equilibrium will be stable and unstable if $R_0 > 1$. For the infected equilibrium we established conditions to ensure the local stability. We need the condition $a \leq d + \frac{a}{T_{max}}[T_2 + I_2]$ to ensure the global stability for this equilibrium. We also established conditions for the occurrence of a Hopf Bifurcation. And we established conditions to ensure the permanence of our system. Moreover we made an estimation for the length of delay to preserve stability depending on the parameters of system (1).

For a non-cytopathic virus ($d = \mu$), we found the sufficient and necessary conditions of the global stability

for the infected equilibrium state of hepatitis infection model (1). We note that

$$T_2 + I_2 = T_0 = \frac{T_{max}}{2a} \left[(a - d) + \sqrt{(a - d)^2 + \frac{4as}{T_{max}}} \right]. \quad (27)$$

Substituting the relation (27) into condition $a \leq d + \frac{a}{T_{max}}[T_2 + I_2]$, we obtain

$$(a - d) \leq \sqrt{(a - d)^2 + \frac{4as}{T_{max}}}.$$

It is clear that the inequality is satisfied for all positive parameter values. From Theorem 4, we obtain the following corollary.

Corollary 1. *Assume that $d = \mu$ and $R_0 > 1$, then the infected equilibrium state E_2 of model (1) is globally asymptotically stable for any $\tau \geq 0$.*

Our analysis shows that if the infection is not cytopathic ($d = \mu$) then nonexistence periodic solutions.

Acknowledgements

This article was supported by UADY under grant FMAT-2012-0004 and Mexican SNI under grants 15284 and 33365.

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